Recombinant human parathyroid hormone 1-84 (Natpara)

National Drug Monograph
May 2016
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1-2]

Description/Mechanism of Action	Recombinant human parathyroid hormone (rhPTH 1-84) is identical to endogenous parathyroid hormone (PTH) and binds PTH-1 receptors in the bone, kidney, and has an indirect effect on calcium reabsorption in the intestine. It increases serum calcium by increasing renal tubular calcium reabsorption, intestinal calcium absorption, and bone turnover.
Indication under Review in this document	rhPTH 1-84 is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. Due to the potential risk of osteosarcoma, rhPTH 1-84 is recommended only for patients who cannot be well controlled on calcium and active vitamin D supplementation alone. rhPTH 1-84 was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations or patients with acute post-surgical hypoparathyroidism.
Dosage Form(s) Under Review	Injection: 25 mcg, 50 mcg, 75 mcg, and 100 mcg
REMS	☒ REMS ☐ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Category C[1]

Executive Summary[1, 3-6]

Efficacy	• rhPTH 1-84 is effective in maintaining serum calcium levels while allowing for decreased utilization of active vitamin D and oral calcium supplementation.[3] • In REPLACE, 54.8% of patients treated with the standard of therapy plus rhPTH 1-84 achieved the triple primary endpoint of a 50% reduction of oral calcium, a 50% reduction of active vitamin D supplementation, and maintenance of an albumin-corrected total serum calcium concentration between 7.5 mg/dL and 10.6 mg/dL at 24 weeks compared to 1 (2.5%) in the standard of care arm alone. The percent difference in response was 52.3% and was statistically significant (95% CI: 40.6% to 64.0%, $p < 0.001$).[3] • In randomized clinical trials (RCT), long-term beneficial reductions of hypercalciuria and renal complications of hypoparathyroidism have not been demonstrated with rhPTH 1-84. While some case reports and RCT subgroups receiving rhPTH 1-34 and rhPTH 1-84 have shown marked improvements in well-being; RCTs have not shown improvement in quality of life (QoL) when comparing rhPTH 1-84 with the standard of care.[4]
Safety	• rhPTH 1-84 has a black box warning for osteosarcoma. It is available in conjunction with a REMS program mandated by the FDA. Risk factors for osteosarcoma include: Paget's disease of the bone, elevations of alkaline phosphatase of unknown etiology, patients with open epiphyses, hereditary disorders which predispose them to osteosarcoma, or prior history of external beam or implant radiation therapy involving the skeleton.[1] • In a prospective 4-year study of rhPTH 1-84, 11 episodes of hypercalcemia in 8 study participants were observed. None of these required hospitalization.[5] • In the phase 3 REPLACE trial, only one severe event of hypercalcemia was

	attributed to the study drug.[3] • During the REPEAT trial, 5 patients were determined to have hypercalcemia events related to rhPTH 1-84 use.[6]
Potential Impact	• The 2015 European Society of Endocrinology Clinical Guidelines recommend supplementation with oral calcium salts and active vitamin D metabolites as the primary treatment for hypoparathyroidism (Evidence: Low).[6] • According to the REPLACE trial, rhPTH 1-84 can reduce the degree of vitamin D and calcium supplementation required to achieve a normal serum calcium level; however, long-term benefits of rhPTH 1-84 have not been demonstrated in clinical trials. rhPTH 1-84 may be considered in patients not able to maintain a normal serum calcium level despite adequate vitamin D and oral calcium supplementation (Evidence: Low).[3] • Vitamin D and oral calcium supplementation requires multiple doses administered several times per day. rhPTH 1-84 is a once daily subcutaneous injection which must be reconstituted prior to administration; the administration device, the Q-Cliq™ pen, is a multiple dose, dual-chamber, glass cartridge containing a lyophilized powder and sterile diluent. As the reconstitution and administration of rhPTH 1-84 is more complex than oral vitamin D and calcium supplementation, the patient's ability to appropriately administer the hormone must be considered prior to use.[1]

Background

Purpose for review

rhPTH 1-84 was approved by the FDA (January 2015) for the treatment of hypoparathyroidism; the purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to considering rhPTH 1-84 for addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Issues to be determined:

- Does evidence support a need for rhPTH 1-84 use?
- Does rhPTH 1-84 offer any advantage over VANF therapies? What safety issues need consideration?
- Does rhPTH 1-84 have properties, which are best managed by the non-formulary process or criteria for use?

Other therapeutic options and adjunct therapy

Formulary Alternatives	Other Considerations
Calcium Carbonate	1,000 – 2,000mg of elemental calcium daily
Calcium Acetate	1,000 – 2,000mg of elemental calcium daily
Calcium Citrate	1,000 – 2,000mg of elemental calcium daily
Vitamin D	25,000 – 200,000IU daily
Calcitriol	1 - 2mcg daily
Adjunct therapy	
Hydrochlorothiazide	25 – 100mg daily
Chlorthalidone	25 – 200mg daily

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (January 2011 to March, 2016) using a combination of the following search terms: parathyroid hormone, PTH 1-84, Natpara and hypoparathyroidism. The search was limited to studies performed in humans and published in the English language. The phase 3 clinical trials published in peer-reviewed journals are included.

Review of Efficacy

- The FDA approval of rhPTH 1-84 was based on four phase 3 studies, which included REPLACE, RACE, RELY and REPEAT. REPLACE, the largest randomized controlled study, focused on hypoparathyroidism and was the pivotal trial for the FDA review. The other 3 trials were not controlled or as large and the efficacy data was consistent with that of the REPLACE study; thus, they will not be reviewed in detail.

REPLACE (CL-11-040): Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism [2, 3]

- REPLACE was a multinational, multicenter, randomized, double blind, placebo-controlled, Phase 3 study that enrolled patients ≥18 years old with hypoparathyroidism. The aim of the trial was to assess the ability of rhPTH 1-84 to maintain serum calcium levels in patients with hypoparathyroidism in the presence of reduced calcium and vitamin D supplementation.
- Key eligibility requirements for subjects to participate in the study: 18-85 years of age; hypoparathyroidism for ≥18 months; on an active vitamin D therapy equivalent to 25mcg of calcitriol; had normal thyroid function or stable thyroid replacement therapy for ≥3 months; had normal 25-hydroxyvitamin D and magnesium levels; had a creatinine clearance of >60 mL/min by the end of the optimization period; and a documented negative pregnancy test along with the willingness to utilize two forms of contraception in applicable female subjects.
- Key exclusionary criteria: hypoparathyroidism caused by calcium sensing receptor (CaSR) mutations; dependent on regular infusion of calcium; history of seizures; prevalent diseases known to affect calcium-phosphate metabolism (e.g., Paget's, severe and chronic cardiac disease, liver or renal disease, poorly controlled diabetes mellitus (HbA1c >8%), etc.); medications known to influence calcium-phosphate metabolism, or a history of radiotherapy within 5 years prior to screening.
- Majority of subjects were female (79%) and white (96%); post-surgical hypoparathyroidism was the most common etiology. Overall, demographics/baseline characteristics were well balanced (Table 1).

Table 1: REPLACE - Demographics and baseline characteristics for subjects administered rhPTH 1-84 daily or placebo; data expressed as number (%) or mean value ± SD unless otherwise specified[2]

Characteristics	rhPTH 1-84 (n = 84)	Placebo (n = 40)
Age	46.6 (12.2)	48.9 (13.7)
Female sex – no. (%)	65 (77.4)	33 (82.5)
Duration of hypoparathyroidism (years)	14.6 (11.2)	11.6 (8.1)
Prescribed active vitamin D metabolite/analog at baseline[a]		
Low dose – no. (%)	6 (6.7)	3 (7.5)
Medium dose– no. (%)	23 (25.6)	12 (30)
High dose – no. (%)	61 (67.8)	25 (62.5)
Prescribed calcium at baseline		
0-2000mg/day	57 (67.9)	29 (72.5)
> 2000mg/day	27 (32.1)	11 (27.5)

[a] For calcitriol: low dose 0-0.25 µg/day, medium dose >0.25-0.5 µg/day, high dose >0.5 µg/day; for alphacalcidol: low dose 0-0.50 µg/day, medium dose >0.50-1.0 µg/day, high dose >1.0 µg/day

- The trial consisted of three periods: optimization, treatment and follow up.
    - Optimization (2 to 16 weeks): Baseline oral calcium and vitamin D doses adjusted to achieve an albumin corrected total serum calcium level between 8.0-9.0 mg/dL. Additionally, magnesium supplementation and thiazide discontinuation occurred if needed.
    - Treatment (24 weeks): Patients were randomized in a 2:1 ratio for daily subcutaneous treatment with rhPTH 1-84 or subcutaneous placebo.
        - Flexible dosing: On day 1, patients had their calcium and vitamin D decreased by 50% and started rhPTH 1-84 50 mcg or placebo. Calcium and vitamin D

supplementation was adjusted if the serum calcium level was below 8 or above 9mg/dL. rhPTH 1-84 doses were increased at the end of the first and fourth weeks, if patients did not achieve independence from active vitamin D and had not reduced the calcium dose to ≤ 500mg/day. Doses were decreased if the patient was hypercalcemic and not using calcium and vitamin D supplementation.
    - Follow up (4 weeks): Discontinuation of randomized therapy and return to pre-trial supplementation.
- Triple component primary endpoint evaluated at 24 weeks included:
    - At least a 50% reduction of oral calcium compared to baseline
    - At least a 50% reduction of active vitamin D doses compared to baseline
    - Maintenance of an albumin-corrected total serum calcium concentration between 7.5mg/dL and 10.6mg/dl
- Key secondary efficacy endpoints included:
    - Percent change in daily calcium supplementation at Week 24
    - Proportion of subjects who achieved independence from active vitamin D supplementation and who utilized a calcium dose of ≤ 500mg/day by Week 24
- Exploratory endpoints included:
    - Change in the 24-hour urine calcium excretion from baseline to Week 24
    - Proportion of patients that maintained a calcium–phosphate product in the normal range of 35-55mg^2/dL^2 at 24 weeks
    - Change in bone turnover and bone mineral density (BMD) as measured by DXA at 24 weeks
- Primary outcome results (Table 2): 46 patients (54.8%) in the rhPTH 1-84 arm achieved the triple primary endpoint at 24 weeks compared to 1 (2.5%) in the placebo arm. The percent difference in response was 52.3% and was statistically significant (95% CI: 40.6% to 64.0%, p < 0.0001).
    - % of patients able to reduce oral calcium by ≥ 50%: 69% rhPTH 1-84 versus 7.5% placebo
    - Percent of patients able to reduce oral active vitamin D by ≥ 50%: 86.9% rhPTH 1-84 versus 45% placebo
    - Percent of patients able to maintain a total serum calcium between 7.5 mg/dL and 10.6 mg/dl: 86.9% rhPTH 1-84 versus 87.5% placebo
- Secondary outcome results:
    - The rhPTH 1-84 group showed a mean decrease of 51.8% (± 45.7%) in calcium supplementation compared to a slight mean increase of 2.4% (± 38.4%) in the placebo group (difference between groups p < 0.001)
    - 36 subjects (41.7%) treated with rhPTH 1-84 were independent of vitamin D supplementation and were receiving calcium doses at ≤ 500mg/day, compared with 1 subject (2.5%) in the placebo group (p < 0.001)
- Exploratory endpoints results:
    - At 24 weeks there was a lower percentage of subjects with a 24-hour urine calcium excretion > 300 mg/24 hour in the rhPTH 1-84 treated patients. However the change was not statistically significant. Only one patient in the placebo group had an elevated calcium-phosphate product
    - Favorable changes in several bone biomarkers without meaningful changes in bone mineral density measured by DXA

Table 2: Summary of Phase 3 Randomized Controlled Clinical Trials supporting the FDA indication for recombinant human parathyroid hormone 1-84 (rhPTH 1-84) [2-3, 6-8]

Study[a]	Design	Dosing (Daily subcutaneous injections)	Study Duration	Number of Subjects	1° Outcome No. (%) (95% CI)	Treatment difference (95% CI) P value
REPLACE[b] (CL-11-040)	Randomized Double-blind Placebo-controlled	rhPTH 1-84 50, 75, and 100 mcg (flexible doses) or placebo	24 weeks	Total: 124[c] rhPTH 1-84: 84[c] Placebo: 40[c]	Outcome[d] 46 (54.8%) (43.5, 65.7) 1 (2.5%) (0.06,13.16)	 52.3 (40.6,64.0) < 0.0001

RACE[e,] (PAR-C10-008)	Open-label	rhPTH 1-84 25, 50, 75, and 100 mcg (flexible doses)	52 weeks + extension (Ongoing)	49	Outcome[f] As of 9/30/14 50% of patients (18/36) met the efficacy endpoint	Not currently published
RELAY (PAR-C10-007)	Randomized Double-blind	rhPTH 1-84 25or 50 mcg (fixed doses)	8 weeks	Total: 42 25 mcg: 19 50 mcg: 23	Outcome[g] 4 (21.1%) (6.1, 45.6) 6 (26.1%) (10.2, 48.4)	 5.0 (-20.6, 30.7) >0.999
REPEAT (PAR-C10-009)	Open-label	rhPTH 1-84 50, 75 and 100mcg (flexible dosing)	24 weeks	24	Outcome[h] 18 (75%)	Not sufficiently powered

[a] Subjects were allowed to participate in more than one trial sequentially.

[b] Landmark pivotal phase 3 trial.

[c] An issue at a study site resulted in the exclusion of data from 10 subjects in REPLACE (The above number of subjects and outcome data was taken from the FRD briefing document and reflects the exclusion).

[d] REPLACE primary endpoint was a 50% reduction of oral calcium and vitamin D doses compared to baseline and maintenance of serum calcium concentration between 7.5 and 10.6 mg/dL at 24 weeks.

[e] Projected completion date was December 2015.

[f] RACE primary endpoint was a ≥50% reduction from baseline in dose of oral calcium supplementation or an oral calcium dose of ≤500 mg, a ≥50% reduction from baseline in dose of oral calcitriol supplementation or an oral calcitriol dose of ≤0.25 µg and an albumin-corrected total serum calcium concentration that is normalized or maintained between 7.5 mg/dL and 10.6 mg/dl

[g] RELAY primary endpoint was a reduction in oral calcium supplementation to ≤ 500 mg/day, a reduction in calcitriol dose to ≤ 0.25 µg/day and an albumin-corrected total serum calcium level between 7.5 mg/dL and 10.6 mg/dl.

[h] REPEAT primary outcome was a 50% reduction from baseline in oral calcium dose or an oral calcium dose of ≤500 mg/day, a ≥50% reduction from baseline in oral calcitriol/alfacalcidol dose or an oral calcitriol dose of ≤0.25 µg/day or alfacalcidol dose of ≤0.50 µg/day, and a total serum calcium concentration that was normalized or maintained (target, 8.0–9.0 mg/dL [2.0−2.2 mmol/L]) compared with baseline value and did not exceed.

RACE (PAR-C10-008): A long-term Open-label Study Investigating the Safety and Tolerability of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH [1-84]), for the Treatment of Adults With Hypoparathyroidism - A Clinical Extension Study [2, 8]

- A phase 3, 12-month open-label extension of REPLACE and RELAY
- Inclusion and exclusion criteria similar to REPLACE
- 49 patients enrolled across 12 centers in the United States received a flexible dosing regimen that initiated with 25 or 50mcg per day rhPTH 1-84 and subsequently up-titrated to 50, 75, or 100mcg per day if vitamin D and calcium supplementation could be reduced
- The primary triple endpoint below was similar to the REPLACE trial.
  - ≥ 50% reduction in oral calcium or ≤ 500mg/day
  - ≥ 50% reduction in active vitamin D dose or ≤ 0.25mcg/day,
  - Albumin-corrected serum calcium ≥1.87mmol/L
- Key results:
  - 50% of patients (18/36) met the efficacy endpoint
  - Serum phosphorus levels showed a mean decrease of 0.22±0.29mmol/L at month 36
  - Albumin-corrected serum calcium levels were maintained both at baseline and month 36
- This extension trial result was constant with the efficacy information in the REPLACE trial, and demonstrates efficacy over a three-year period.

RELAY (PAR-C10-007): Study of Safety and Efficacy of a rhPTH [1-84] of Fixed Doses of 25 and 50mcg in Adults With Hypoparathyroidism (RELAY) [2, 7]

- A phase 3, 8-week randomized double blind extension study to investigate the safety and efficacy of rhPTH
- The main inclusion criterion was the completion of the REPLACE trial, other inclusion and exclusion criteria were similar to REPLACE.

- Forty patients with a history of hypoparathyroidism were randomized to receive either a 25mcg or 50mcg dose for 8 weeks.
- Patients ≥ 65 years old (3) were all treated with the lower 25mcg dose.
- The primary triple endpoint, as seen below, was similar to the endpoint utilized in the REPLACE trial.
    - Reduction of oral calcium supplementation to ≤ 500mg/day
    - Reduction in calcitriol dose to ≤ 0.25mcg/day
    - An albumin-corrected total serum calcium level between 7.5mg/dL and the upper limit of the laboratory normal range
- A greater percentage of subjects in the 50mcg-dosing arm achieved the triple endpoint.
- Efficacy information was similar to that seen in REPLACE; see Table 2 for results of the trial.

REPEAT (PAR-C10-009): AN OPEN-LABEL EXTENSION STUDY OF PARATHYROID HORMONE rhPTH (1-84) IN ADULTS WITH HYPOPARATHYROIDISM [2, 6]

- A phase 3, 24-week open-label extension trial of REPLACE
- Twenty four subjects enrolled across 3 centers in Hungary were comprised of patients who completed REPLACE to evaluate safety and continued benefits of rhPTH 1-84. This study included 24 patients 23 of which completed the REPLACE trial. Sixteen of the subjects were previously treated with rhPTH 1-84 and 8 were treatment naïve.
- The primary triple endpoint, as seen below, was similar to the endpoint utilized in the REPLACE trial
    - ≥ 50% reduction in oral calcium supplementation or oral calcium dose of ≤500mg/day
    - ≥ 50% reduction in oral calcitriol/alfacalcidol supplementation or an oral calcitriol dose of ≤ 0.25mcg/day or alfacalcidol dose of ≤0.50mcg/day
    - Total serum calcium concentration normalized or maintained
- Key results:
    - 75% of patients (95% CI, 53.3%–90.2%) achieved the study endpoint.
    - Mean serum and urinary calcium decreased by 2.3%±11% and 5.1%±60% respectively.
    - Mean serum phosphate levels decreased by a mean of 0.7±0.7mg/dL at 24 weeks.
    - Mean calcium phosphate product decreased by 7.8±7.0$mg^{2/}dL^2$ at 24 weeks.
    - Among study patients as a whole, bone mineral density measurements showed minimal changes from baseline at Week 24.
- Overall the information from the REPEAT trial was consistent with the REPLACE trial.

PTH (1-84) Administration Reverse Abnormal Bone-Remodeling Dynamics And Structure In Hypoparathyroidism [9]

- 64 subject, non-placebo controlled study that occurred across two sites
- Subjects received rhPTH 1-84 100mcg injections every other day for 24 months
- Key finding included:
    - Reduced trabecular width from 144± 34 at baseline to 128±34 (p=0.03)
    - Increased trabecular number from 1.74±0.34/mm to 2.07±0.05/mm (p=0.02)
    - Increased Cortical porosity from 7.45±3% to 9.2%±2.4% (p=0.03)
    - BMD decreased in response to rhPTH 1-84.
- In this trial rhPTH 1-84 increases remodeling in both trabecular and cortical compartments and improves abnormal skeletal properties.
    - Peak effect was noted at 5 to 9 months; however, there was a trend toward baseline at 24 months.
        - The phase 3 trials also found a trend of bone indices toward baseline over time, but did not correlate those results with meaningful clinical changes. The current information may suggest a normalization of bone metabolism during treatment, however, long-term data is lacking.

Quality of Life Analysis: [10, 11]

- QoL measures were investigated through two main trials:
    - Sikjaer et al. evaluated the QoL changes in 62 patients utilizing standard of care plus rhPTH 1-84 or placebo over 24 weeks. QoL was evaluated at baseline and the end of the

study using the Short Form Questionnaire 36 version 2 (SF-36v2) and the WHO-5 Well-Being Index survey (WHO-5).
    - rhPTH 1-84 caused a slight but significant deleterious effect on muscle strength.
    - QoL improved after 6 months of treatment, but the increase was evident in both the treatment and placebo groups. There was no difference in QoL improvement between groups.
        - The authors stated the lack of QoL changes may be due to the short half-life of rhPTH 1-84 and frequent hypercalcemia was noted.
- Cusano et al. evaluated the QoL changes in 69 patients utilizing standard of care plus rhPTH 1-84 over 5 years (non-placebo controlled). QoL was evaluated baseline and following treatment rhPTH 1–84 at months 2, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 using the RAND 36-Item Short Form (SF-36) Health Survey (version 1.0).
    - Physical component summary (PCS) score improved at 2 months and remained significantly improved through 5 years.
    - Mental component summary (MCS) score improved at 2 months remained improved throughout the duration of the study.

European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults[4]

- The panel recommended against routine use of rhPTH 1-84. They note that normal calcium levels can be achieved using rhPTH 1-84 and that treatment reduces the degree of vitamin D and calcium supplementation required. However, the long-term beneficial reduction of hypercalciuria/renal complications or increased QoL has not been demonstrated.

Potential Off-Label Use

- This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

- A potential off-label use is to increase bone mineral density in postmenopausal women with osteoporosis. NPS Pharmaceuticals previously submitted a New Drug Application (NDA) with a requested indication for osteoporosis treatment in post-menopausal women at high risk of bone fracture. This was submitted under the trade name Preos. The FDA requested two safety concerns be addressed. Subsequently, NPS Pharmaceuticals withdrew the NDA.[2] Since this is not an approved use and the application for this indication has been withdrawn, this monograph will focus on the FDA approved indication listed above.

Safety[1-3, 5-8]

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• **Osteosarcoma:** rhPTH 1-84 may cause an increased risk of osteosarcoma. Potential risk of osteosarcoma was observed in rats and was both dose and duration dependent. This was observed in doses of rhPTH 1-84 between 3 and 71 times the exposure levels compared to a human receiving a 100 mcg dose of rhPTH 1-84. • Use should be avoided in patients at an increased risk for osteosarcoma, such as patients with Paget's disease of bone or elevations of alkaline phosphatase of unknown etiology, patients with open epiphyses, hereditary disorders which predispose them to osteosarcoma, or with prior history of external beam or implant radiation therapy involving the skeleton. • **REMS program:** Because of the potential risk of osteosarcoma, rhPTH 1-84 is available only through restricted distribution under a Risk Evaluation Mitigation Strategy (REMS) program.

Contraindications	• None
Warnings/Precautions	• Hypercalcemia: Severe hypercalcemia has been reported. The risk is highest when starting or titrating the dose of rhPTH 1-84. Two patients in the rhPTH 1-84 group in one of the clinical trials required IV fluid administration due to hypercalcemia. • Hypocalcemia: Severe hypocalcemia has been reported. The risk is highest when rhPTH 1-84 is withheld, missed, or stopped suddenly. However, hypocalcemia is possible at any time. • Risk of Digoxin Toxicity with Concurrent Use of Digitalis Compounds: Calcium levels affect inotropic effects of digoxin and hypercalcemia may increase the risk of digoxin toxicity with concurrent use.

Safety Considerations

- In a prospective 4-year study of 27 patients evaluating safety and efficacy of rhPTH 1-84, 11 episodes of hypercalcemia in 8 study participates were observed. Of these, most were in the first 6 months of treatment and resolved with calcium and vitamin D adjustments; none required hospitalization. Also noted in the study were 2 fractures and 1 episode of nephrolithiasis. The most common adverse events (AEs) were musculoskeletal, gastrointestinal, and genitourinary. Events requiring hospitalizations included hypocalcemia, dehydration and one patient with right flank pain. [5]
- In the phase 3 REPLACE trial, serious AEs classified as mild 1 (1%) vs. 1 (2%), moderate 3 (3%) vs. 2 (5%), and severe 6 (7%) vs. 1 (2%) were observed in the treatment and placebo groups respectively. Severe events were classified according to severity and included hypocalcemia, hypercalcemia, pancreatitis, cerebrovascular accident, and diarrhea. All cases were self-resolving except cerebrovascular accident. Hypercalcemia was the only AE that was attributed to the study drug, which did not lead to discontinuation of treatment.[3]
- In the REPEAT trial, 22 of 24 (92%) enrolled patients reported AEs with most of mild or moderate severity; none discontinued the study due to AEs. The most frequently observed events were hypoesthesia, muscle spasms, decreased vitamin D, hypercalcemia, fatigue, headache, and hypocalcemia. Five patients were determined to have AEs related to rhPTH 1-84 treatment, of these, 7 events were hypercalcemia and 5 out of 7 were of mild to moderate severity.[6]
- No serious AEs were reported during the RELAY trial. The most frequently reported AEs in either group were paresthesia, nausea, muscle spasms, fatigue, headache, hypercalcemia, pollakiuria, arthralgia, and palpitations. Limited information is available regarding this study as it has not been published.[7]
- During the RACE trial, 48 patients (98%) reported AEs. The most commonly reported events were hypocalcemia, muscle spasms, and nausea. Nine patients had a serious adverse event, but none were attributed to rhPTH 1-84 treatment. Limited information is available regarding this study; only the abstract is available at this time.[8]

Adverse Reactions

Common adverse reactions	rhPTH 1-84 (events that occurred in ≥ 5% of study participants and that occurred more commonly in the rhPTH 1-84 arm compared to placebo): paresthesia, hypocalcemia, headache, hypercalcemia, nausea, hypoesthesia, diarrhea, vomiting, arthralgia, hypercalcuria, extremity pain, upper respiratory tract infection, upper abdominal pain, sinusitis, blood 25-hydroxycholecalciferil decreased, hypertension, hypoaesthesia, facial and neck pain.[1]
Death/Serious adverse reactions	No deaths were reported in the phase 3 REPLACE trial or other clinical trials. The REPLACE trial reported adverse events of the highest severity: mild 25 (28%) vs. 15 (34%), moderate 44 (3%) vs. 24 (55%), and severe 15 (17%) vs. 5 (11%) in the treatment and placebo groups respectively. One patient was taken to the emergency room and released the same day after being treated for hypercalcemia. Hypercalcemia was the only event attributed to rhPTH 1-84 use. RACE reported 9 patients with a serious AE, but none were considered treatment related.[2,3]

Discontinuations due to adverse reactions	In the REPLACE trial, three patients in the rhPTH 1-84 group discontinued treatment due to AEs. One patient had several AEs, of which some were deemed to be treatment related. The other two patients had worsening hypertension and cerebrovascular accident, which were not thought to be treatment related.[3]
Other Adverse Events	Immunogenicity: use of rhPTH 1-84 may cause development of antibodies. One patient had a moderate injection site hematoma that started two weeks after initiating rhPTH 1-84. The reaction intensity decreased to mild over time, but persisted for the treatment duration. Antibody development did not seem to affect efficacy or safety during clinical trials. However, long-term significance of the AE was reported to be unknown. [1,3]

Pharmacodynamics/Pharmacokinetics

Table 3: Pharmacokinetics and dynamics of rhPTH 1-84[1,12]

Absorption	An absolute bioavailability of 53% when administered subcutaneously.
Distribution	Volume of distribution of 5.35L at steady state.
Metabolism	Clearance of PTH 1-84 is primarily a hepatic process with a lesser role played by the kidneys.
Elimination	Most of the rhPTH 1-84 is cleaved by cathepsins in the liver. A small amount of rhPTH 1-84 binds to physiologic PTH-1 receptors in the kidney but most is filtered at the glomerulus. C-terminal fragments are also cleared efficiently by glomerular filtration.
Half-life	3.02 hours for the 50mcg dose and 2.83 hours for the 100mcg dose.
Onset and Duration	Mean peak serum calcium levels are reached between 10 and 12 hours following a single subcutaneous injection and the increase in serum calcium above baseline is sustained for more than 24 hours after administration.
Mean T-Max	Peak plasma concentrations occur within 5 to 30 minutes and a second usually smaller peak occurs at 1 to 2 hours.

- *Based on the above parameters rhPTH 1-84 does not mimic the endogenous release pattern of the parathyroid gland. The different release patterns may alter the effect seen in vivo between the hormone and the synthetic analog. One manifestation of this difference is the reduction in urinary calcium excretions, which is no longer seen 10-12 hours after administration. This is attributed to the short half-life.*

Drug-Drug Interactions[1]

Alendronate

Concomitant use with rhPTH 1-84 is not recommended as it can result in a reduced calcium-sparing effect, which may interfere with the normalization of serum calcium. Co-administration may decrease the effectiveness of rhPTH 1-84.

Digoxin (Cardiac Glycosides)

Co-administration with rhPTH 1-84 increases the risk of digoxin toxicity. This occurs if hypercalcemia develops due to transient increases in calcium caused by rhPTH 1-84. If used concomitantly, monitor serum calcium, digoxin levels, and evaluate the patient for signs and symptoms of digoxin toxicity. Adjustment of either digoxin and/or rhPTH 1-84 may be necessary.

Risk Evaluation

As of December 10, 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
REMS requirements	• REMS Certification for prescribers of rhPTH 1-84 • Required items to complete for prescriber certification can be found www.NatparaREMS.com

- Each patient must be counseled on the potential benefits and risks of rhPTH 1-84 use
- The Patient-Prescriber Acknowledgment Form (PPAF) for each patient and prescriber must be competed
- A certified and contracted pharmacy must dispense rhPTH 1-84

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Parathyroid hormone SC 25, 50, 75, 100 mcg cartridge	None	None	None	Teriparatide Paraldehyde
Natpara	None	None	None	Natroba

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

Patient education for use of rhPTH 1-84 is provided by a nurse prior to initiation as part of the REMS requirements.

Patient education regarding proper storage and administration is provided by a nurse. This nurse education is part of the REMS requirement, provided by the contracted pharmacy and included in the prescription ordering process.

Information regarding ordering and the referral form can be found at the following web address: https://vaww.cmopnational.va.gov/cmop/PBM/Special%20Handling%20Drugs/Forms/AllItems.aspx?RootFolder=%2Fcmop%2FPBM%2FSpecial%20Handling%20Drugs%2FNATPARA%20%28Parathyroid%20Hormone%20for%20Injection%29&FolderCTID=0x0120003A2D7D9A5E1F5340B4F2DD475DE7993A&View={27957A0A-568E-4C57-A1E4-6678840ABCF7}.

Dosing and Administration[1, 13]

rhPTH 1-84 is administered using the reusable Q-Cliq™ pen. It is supplied in a multiple dose, dual-chamber, glass cartridge containing a sterile lyophilized powder and a sterile diluent for reconstitution. Each cartridge contains 14 doses and a dose indicator displays the number of doses remaining. The medication should be stored in the refrigerator both before and after reconstitution. It must be discarded 14 days following reconstitution. Refer to the package insert for additional information.

Treatment goals for rhPTH 1-84 therapy include maintaining the serum calcium level within the lower portion of the normal range (approximately 8-9 mg/dL), discontinuation of active vitamin D, and reduction of the calcium supplementation needed to meet the patient's daily requirement.

Dosing of rhPTH 1-84 by subcutaneous injection should be individualized based on the total corrected serum calcium and 24-hour urine calcium excretion. The minimum dose to prevent hypocalcemia and hypercalcuria is recommended. In most cases, this is the one that maintains serum calcium between 8 and 9 mg/dL without supplementation or use of active forms of vitamin D and is sufficient to meet the patient's daily requirements.

Before beginning rhPTH 1-84, sufficient stores of 25-hydroxyvitamin D should be confirmed. In addition, the total corrected serum calcium must greater than 7.5mg/dL prior to initiating rhPTH 1-84.

Administer rhPTH 1-84 by subcutaneous injection in the thigh (alternating thighs daily):

Initial Dosing: 50mcg

- If total corrected serum calcium is greater than 7.5mg/dL and the patient is on active forms of vitamin D, the active vitamin D dose should be reduced by 50%.
- If the patient is using calcium supplementation, the dose of calcium should be maintained.

- A serum calcium level should be obtained between 3 and 7 days following initiation of rhPTH 1-84.
- Either the dose of active vitamin D and/or the calcium supplement dose should be adjusted based on the serum calcium level obtained during this interval and any clinically correlated symptoms. The adjustments listed below (Table 4) are those suggested by the manufacturer and are found in the package insert. The adjustment steps should be repeated until treatment goals are achieved.

Table 4: rhPTH 1-84 dosing adjustments[1]

	Adjust First	Adjust Second
Serum Calcium	**Active Vitamin D Forms**	**Calcium Supplement**
Above the Upper Limit of Normal (10.6 mg/dL)	Decrease or Discontinue*	Decrease
Greater than 9 mg/dL **and below** the Upper Limit of Normal (10.6 mg/dL)	Decrease or Discontinue*	No change or decrease if active vitamin D has been discontinued
Less than or equal to 9 mg/dL **and above** 8 mg/dL	No change	No change
Lower than 8 mg/dL	Increase	Increase
*Discontinue in patients receiving the lowest available dose		

Dose Adjustments

- The dose may be adjusted in 25mcg increments every 4 weeks to a maximum of 100mcg per dose. Titration should occur if the corrected total serum calcium cannot be maintained at a level greater than 8 mg/dL without the use of active vitamin D and/or calcium supplementation.
- If total corrected serum calcium is greater than 9mg/dL on multiple occasions after discontinuation of active vitamin D and calcium supplementation has been reduced to the amount adequate to meet daily requirements, the dose of rhPTH 1-84 may be reduced to 25mcg per day.
- After any dose adjustments, clinical response and serum calcium should be monitored.

Maintenance Dosing

- Maintenance dosing should be the minimum rhPTH 1-84 dose required to maintain total corrected serum calcium between approximately 8 and 9 mg/dL in the presence of calcium supplementation adequate to meet daily requirements but without the use of active forms of vitamin D.
- Serum calcium and 24-hour urinary calcium excretion should be monitored according to the standard of care.

Interruption or Discontinuation

- Severe hypocalcemia may result from abrupt interruption or discontinuation of rhPTH 1-84.
- Active vitamin D and calcium supplementation should be resumed or the doses should be increased, if indicated when patients interrupt or discontinue rhPTH 1-84.
- Serum calcium as well as signs and symptoms of hypocalcemia should be monitored.

Missed Dose

- If a dose of rhPTH 1-84 is missed, it should be administered as soon as possible and if hypocalcemia occurs, exogenous calcium should be taken.[1]

Monitoring

- The manufacturer does not provide any specified interval for monitoring. However, a treatment guideline from the European Society of Endocrinology recommends monitoring calcium, magnesium, phosphate, creatinine, and assessment of symptoms of hypo and hypercalcemia at regular intervals, such as every 3 to 6 months. In addition, monitoring the 24-hour urinary calcium excretion at a regular interval, such as yearly or every other year.
- Following dose changes, weekly or every other week laboratory monitoring is recommended.[11]

Special Populations (Adults)[1]

	Comments
Elderly	• Insufficient study in patients over the age of 65 is available to determine if response differs from younger patients. The manufacturer provides no specific dose adjustments.
Pregnancy	• Category C pregnancy rating: No adequate, well-controlled trials in pregnant women have been conducted. Use during pregnancy only if potential benefit to the mother outweighs risk to the fetus.
Lactation	• Excretion in human breast milk is unknown.
Renal Impairment	• There are no dosing adjustments provided in the manufacturers labeling (has not been studied in a sufficient number of patients with moderate or severe renal impairment). Conversion of 25-hydroxy vitamin D to 1, 25-dihydroxy vitamin D is dependent on renal function. rhPTH 1-84 is eliminated by the kidneys and maximum drug levels were shown to increase with renal impairment. The mean maximum concentration (Cmax) and exposure, measured using area under the curve (AUC), was increased in 16 patients with mild (60-90ml/min) or moderate renal impairment (30-60ml/min). Corrected serum calcium should be monitored.
Hepatic Impairment	• No dosage adjustment for rhPTH 1-84 is recommended for patients with mild to moderate hepatic impairment.
Pharmacogenetics/genomics	• No data identified.[1]

Projected Place in Therapy[5, 8, 13-17]

- Hypoparathyroidism is an uncommon endocrine disorder; estimated 60,000-115,000 individuals in the United States have this diagnosis. It can be acquired or hereditary. Acquired hypoparathyroidism is generally the result of trauma to the parathyroid gland during head or neck surgeries. Surgically induced hypoparathyroidism occurs in between 0.12–4.6% of anterior neck operations, is transient in most cases, but can be permanent. Less common is an autoimmune pathogenesis, which commonly involves a mutation in the autoimmune regulator of endocrine function (AIRE) gene. The incidence rate of hypoparathyroidism within the VA population is comparable to that of the general population in the United States. In FY2015, 1,295 Veterans had an ICD-9 or ICD-10 code indicating hypoparathyroidism. In the Veteran population, the most common causes of chronic hypoparathyroidism are due to complications from head or neck surgery.
- Hypoparathyroidism is characterized by a low level of albumin corrected serum calcium and a low or undetectable PTH concentration (<20 pg/mL) that should be confirmed on two separate occasions at least two weeks apart. Parathyroid hormone plays a key role in calcium and phosphate homeostasis. Low levels of PTH results in decreased calcium reabsorption in the kidney, decreased calcium mobilization from the bones, and decreased calcium absorption in the intestines. Mineral disturbances such as hypocalcaemia, hyperphosphatemia, hypercalciuria and reduced levels of active vitamin D are attributable to the previously mentioned alteration in homeostasis. The majority of abnormal clinical indices are attributable to reduced calcium levels. The spectrum of signs and symptoms resulting from hypoparathyroidism can range from asymptomatic disease to patients with life-threatening complications. Chronic manifestations attributed to hypoparathyroidism can include: hearing loss, immunodeficiency, skeletal, dental, cardiac abnormalities, dermal changes, and renal complications.
- The treatment goal in hypoparathyroidism is to correct serum calcium levels to the low end or slightly below the normal range, to prevent symptoms and to mitigate adverse effects. Hypoparathyroidism is

the last major endocrine disorder not primarily treated with exogenous hormone replacement. The hallmark treatment is combination calcium and vitamin D supplementation. However, calcium and vitamin D supplementation may not treat all components of hypoparathyroidism.

- rhPTH 1-84 is the first hormone analog developed and approved in the United States for the treatment of hypoparathyroidism in conjunction with calcium and vitamin D supplementation. In REPLACE, rhPTH 1-84 was able to maintain serum calcium levels despite significant reductions in calcium and vitamin D supplementation. A little over 40% of patients were able to maintain calcium levels without vitamin D and a calcium dose of 500mg/day. rhPTH 1-84 is fairly well tolerated and provides an alternative treatment for patients who are unable to maintain adequate calcium levels on active forms of vitamin D and calcium alone. This treatment is not without risks and as part of the REMS program, a discussion of the risks versus benefits between provider and patient should occur.
- The most serious risk, as indicated by a black box warning, is osteosarcoma. Due to the risk of osteosarcoma, thorough screening prior to beginning treatment with rhPTH 1-84 for risk factors that would predispose a patient to osteosarcoma should be completed. Any patients who are found to have these risks should be excluded from rhPTH 1-84 therapy.
- The most common AEs are hypo and hypercalcemia. The greatest risk for an AE, which inherently occurs in hypoparathyroidism, is during treatment initiation, discontinuation, and dose adjustments. As a result, close monitoring is warranted at these times.
- Current evidence strongly supports the ability of rhPTH 1-84 to maintain serum calcium levels in the normal range despite reductions in oral vitamin D and calcium supplementation. However, the evidence from the phase 3 studies failed to demonstrate beneficial effects on renal complications or hypercalciuria and the skeletal effects of rhPTH 1-84 remain controversial. A guideline published by the European Society of Endocrinology recommends against the routine use of replacement therapy with PTH analogues. The guideline indicates that, while maintenance of calcium can be achieved with rhPTH 1-84, the long-term benefits of therapy have not been determined. Additional data is required to determine the long term benefit of rhPTH 1-84 with respect to change in bone turnover, bone mineral density and the impact rhPTH 1-84 has on urine calcium excretion.
- rhPTH 1-84 may provide benefit for a small subset of patients and should be reserved for those patients unable to maintain appropriate serum calcium levels utilizing traditional supplementation with active vitamin D and oral calcium. Therapies to mitigate complications of hypoparathyroidism, such as hydrochlorothiazide, should be utilized prior to initiation of rhPTH 1-84, as the current data is inconclusive regarding the benefit of direct hormone replacement.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010; 153:194-199.